



IC06 Rec'd PCT/PTO 14 SEP 2005

#3

Applicant:

Hagit ELDAR-FINKELMAN

Serial No.: 10/538,171

Filed: June 9, 2005

For: GLYCOGEN SYNTHASE KINASE-3 INHIBITORS

Examiner:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

~~~~~

Group Art Unit: Not yet assigned

Attorney  
Docket: 29724

## INFORMATION DISCLOSURE STATEMENT

Sir:

Enclosed is a PTO Form 1449 which lists citations which may be material to the patentability and examination of the above identified application. Also enclosed are copies of the references cited. These are submitted in compliance with the duty of disclosure defined in 37 CFR 1.56. The Examiner is requested to make these citations of official record in this application.

This Information Disclosure Statement under 37 CFR 1.56 is not to be construed as a representation that a search has been made, that additional matter which is material to the examination of this application does not exist, or that any or more of these citations constitutes prior art.

Respectfully submitted,

Martin D. Moynihan

Martin Moynihan  
Registration No. 40,338

Dated: August 24, 2005





PTO/SB/08b (08-03)

Approved for use through 06/30/2006. OMB 0651-0031

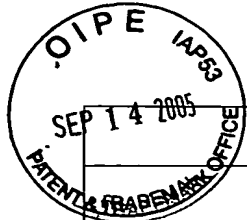
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

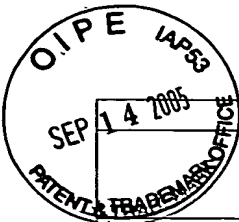
| Substitute for form 1449A/PTO                                                                            |                       |                                                                                                                                                                                                                                                                  |  | Complete if Known      |                       |
|----------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|------------------------|-----------------------|
| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br><br><i>(use as many sheets as necessary)</i> |                       |                                                                                                                                                                                                                                                                  |  | Application Number     | 10/538,171            |
|                                                                                                          |                       |                                                                                                                                                                                                                                                                  |  | Filing Date            | June 9, 2005          |
|                                                                                                          |                       |                                                                                                                                                                                                                                                                  |  | First Named Inventor   | ELDAR-FINKELMAN Hagit |
|                                                                                                          |                       |                                                                                                                                                                                                                                                                  |  | Group Art Unit         | Not yet assigned      |
|                                                                                                          |                       |                                                                                                                                                                                                                                                                  |  | Examiner Name          |                       |
| Sheet                                                                                                    |                       | Of                                                                                                                                                                                                                                                               |  | Attorney Docket Number | 29724                 |
| OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS                                                        |                       |                                                                                                                                                                                                                                                                  |  |                        |                       |
| Examiner Initials                                                                                        | Cite No. <sup>1</sup> | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.    |  |                        | T <sup>2</sup>        |
|                                                                                                          | 18                    | Donella-Deana et al. "Dephosphorylation of Phosphopeptides by Colcineurin (Protein Phosphatase 2B)", Eur. J. Biochem., 219(1-2): 109-117, 1994. Tab.1, 2.                                                                                                        |  |                        |                       |
|                                                                                                          | 19                    | Otaka et al. "Synthesis and Application of N-Box-L-2-Amino-4-(Diethylphosphono)-4,4-Difluorobutanoic Acid for Solid-Phase Synthesis of Nonhydrolyzable Phosphoserine Peptide Analogues", Tetrahedron. Lett., 36(6): 927-930, 1995.                               |  |                        |                       |
|                                                                                                          | 20                    | Othaka et al. "Development of New Methodology for the Synthesis of Functionalized $\alpha$ -Fluorophosphonates and Its Practical Application to the Preparation of Phosphopeptide Mimetics", Chem. Commun., 12: 1081-1082, 2000.                                 |  |                        |                       |
|                                                                                                          | 21                    | Pap et al. "Role of Glycogen Synthase Kinase-3 in the Phosphatidylinositol 3-Kinase/Akt Cell Survival Pathway", J. Biol. Chem., 273: 19929-19932, 1998.                                                                                                          |  |                        |                       |
|                                                                                                          | 22                    | Phiel "Molecular Targets of Lithium Action", Annu. Rev. Pharmacol. Toxicology, 41: 789-813, 2001.                                                                                                                                                                |  |                        |                       |
|                                                                                                          | 23                    | Barrett et al. "Proteinase Inhibitors", Research Monographs in Cell and Tissue Physiology, V-XXII, 1986.                                                                                                                                                         |  |                        |                       |
|                                                                                                          | 24                    | Roller et al. "Potent Inhibition of Protein-Tyrosine Phosphatase-1B Using the Phosphotyrosyl Mimetic Fluoro-O-Malonyl Tyrosine (FOMT)", Bioorg. Med. Chem. Lett., 8(16): 2149-2150, 1998.                                                                        |  |                        |                       |
|                                                                                                          | 25                    | Rubinfeld et al. "Binding of GSK3Beta to the APC-Beta-Catenin Complex and Regulation of Complex Assembly", Science, 272(5264): 1023-1026, 1996.                                                                                                                  |  |                        |                       |
|                                                                                                          | 26                    | Sambrook et al. "Molecular Cloning: A Laboratory Manual", Cold Spring Harbour Press, 2nd Ed., V-XXXII, 1989.                                                                                                                                                     |  |                        |                       |
|                                                                                                          | 27                    | Schiller et al. "Synthesis for Side-Chain Cyclized Peptide Analogs on Solid Supports", Int. J. Peptide Protein Res., 25: 171-177, 1985.                                                                                                                          |  |                        |                       |
|                                                                                                          | 28                    | Shapiro et al. "Combined Fmoc-Alloc Strategy for A General SPPS of Phosphoserine Peptides: Preparation of Phosphorylation-Dependent Tau Antisera", Bioorg. Med. Chem., 5(1): 147-156, 1997.                                                                      |  |                        |                       |
|                                                                                                          | 29                    | Sherman et al. "Compatibility of Thioamides With Reverse Turn Features: Synthesis and Conformational Analysis of Two Model Cyclic Pseudopeptides Containing Thioamides as Backbone Modifications", Journal of the American Chemical Society, 112: 433-441, 1990. |  |                        |                       |
|                                                                                                          | 30                    | Shulman et al. "Quantitation of Muscle Glycogen Synthesis in Normal Subjects and Subjects With Non-Insulin-Dependent Diabetes by <sup>13</sup> C Nuclear Magnetic Resonance Spectroscopy", New England Journal of Medicine, 322(4): 223-228, 1990.               |  |                        |                       |
|                                                                                                          | 31                    | Stambolic et al. "Lithium Inhibits Glycogen Synthase Kinase-3 Activity and Mimics Wingless Signalling in Intact Cells", Curr. Biol., 6: 1664-1668, 1996.                                                                                                         |  |                        |                       |
|                                                                                                          | 32                    | ter Haar et al. "Structure of GSK-3 Beta Reveals A Primed Phosphorylation Mechanism", Nat. Struct. Biol., 8(7): 593-596, 2001.                                                                                                                                   |  |                        |                       |
|                                                                                                          | 33                    | Thomas "Excitatory Amino Acids in Health and Disease", J. Am. Geriatr. Soc., 43: 1279-1289, 1995.                                                                                                                                                                |  |                        |                       |
|                                                                                                          | 34                    | Thorsett et al. "Dipeptide Mimics. Conformationally Restricted Inhibitors of Angiotensin-Converting Enzyme", Biochem. Biophys. Res. Commun., 111(1): 166-171, 1983.                                                                                              |  |                        |                       |
|                                                                                                          | 35                    | Tong et al. "Activation of Glycogen Synthase Kinase-3 Beta (GSK-3 Beta) by Platelet Activating Factor Mediates Migration and Cell Death in Cerebellar Granule Neurons", Eur. J. Neurosci., 13: 1913-1922, 2001.                                                  |  |                        |                       |
|                                                                                                          | 36                    | Veber et al. "Conformationally Restricted Bicyclic Analogs of Somatostatin", Proc. Natl. Acad. Sci. USA, 75(6): 2636-2640, 1978.                                                                                                                                 |  |                        |                       |



|    |                                                                                                                                                                                                                                                              |  |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| 37 | Welsh et al. "Glycogen Synthase Kinase-3 Is Rapidly Inactivated in Response to Insulin and Phosphorylates Eukaryotic Initiation Factor Eif-2B", <i>Biochem. J.</i> , 294(Pt 3): 625-629, 1993.                                                               |  |
| 38 | Wiemann et al. "Synthesis of Suitably Protected Hydroxymethylene Phosphonate- and 'Phosphat Phosphonate'-Analogues of Phosphoserine and Their Incorporation Into Synthetic Peptides", <i>Tetrahedron</i> , 56: 1331-1337, 2000.                              |  |
| 39 | Ye et al. "L-O-(2-Malonyl)Tyrosine: A New Phosphotyrosyl Mimetic for the Preparation of Src Homology 2 Domain Inhibitory Peptides", <i>J. Med. Chem.</i> , 38(21): 4270-4275, 1995.                                                                          |  |
| 40 | Eldar-Finkleman et al. "The Insulin Mimetic Action of Glycogen Synthase Kinase-3 Inhibitors", <i>Diabetologia</i> , 45(Suppl.2): A 70, 38th Annual Meeting for the European Association for the Study of Diabetes (EASD), Budapest, Hungary, 2002. Abstract. |  |
| 41 | Plotkin et al. "Insulin Mimetic Action of Synthetic Phosphorylated Peptide Inhibitors of Glycogen Synthase Kinase-3", <i>Journal of Pharmacology and Experimental Therapeutics</i> , 305(3): 974-980, 2003.                                                  |  |
| 42 | Leclerc et al. "Indirubins Inhibit Glycogen Synthase Kinase-3 $\beta$ and CDK5/P25, Two Proteins Kinases Involved in Abnormal Tau Phosphorylation in Alzheimer's Disease", <i>The Journal of Biological Chemistry</i> , 276(1): 251-260, 2001.               |  |
| 43 | Hotamisligil et al. "IRS-1-Mediated Inhibition of Insulin Receptor Tyrosine Kinase Activity in TNT- $\alpha$ - and Obesity-Induced Insulin Resistance", <i>Science</i> , 271: 665-667, 1996.                                                                 |  |
| 44 | Tanti et al. "Serine/Threonine Phosphorylation of Insulin Receptor Substrate 1 Modulates Insulin Receptor Signaling", <i>The Journal of Biological Chemistry</i> , 269(8): 6051-6057, 1994.                                                                  |  |
| 45 | Fahraeus et al. "Inhibition of PRB Phosphorylation and Cell-Cycle Progression by A 20-Residue Peptide Derived From P16 CDKN2/INK4A", <i>Current Biology</i> , 6(1): 84-91, 1996.                                                                             |  |
| 46 | Mitchell et al. "Heat-Stable Inhibitor Protein Derived Peptide Substrate Analogs: Phosphorylation by cAMP-Dependent and cGMP-Dependent Protein Kinases", <i>Am. Chemical Soc.</i> , 1994.                                                                    |  |
| 47 | Maniatis "Signal Transduction: Catalysis by A Multiprotein I $\kappa$ B Kinase Complex", <i>Science</i> , 278(5339): 818, 1997. Extract.                                                                                                                     |  |
| 48 | American Diabetes Association "Standards of Medical Care for Patients With Diabetes Mellitus", <i>Diabetes Care</i> , 17(6): 616-623, 1994.                                                                                                                  |  |
| 49 | Hawiger "Non-Invasive Intracellular Delivery of Functional Peptides", <i>Curr. Opin. Chem. Biol.</i> , 3: 89-94, 1999.                                                                                                                                       |  |
| 50 | Moreno et al. "Glycogen Synthase Kinase 3 Phosphorylation of Different Residues in the Presence of Different Factors: Analysis on TAU Protein", <i>Mol.Cell.Biochem.</i> , 165(1):47-54, 1996. Tab.1.                                                        |  |
| 51 | Correll et al. "Inhibition of GSK3 Beta Mediates Cell Survival ... Society For Neuroscience Abstracts" 25(2): 1519, 1999. Abstract No. 605.8.                                                                                                                |  |
| 52 | Oelrichs et al. "Unique Toxic Peptides Isolated From Sawfly Larvae in Three Continents", <i>Toxicon</i> , 37(3): 537-544, 1999. Fig.3.                                                                                                                       |  |
| 53 | Fiol et al. "Ordered Multisite Protein Phosphorylation. Analysis of Glycogen Synthase Kinase-3 Action Using Model Peptide Substrates", <i>The Journal of Biological Chemistry</i> , 265(11): 6061-6065, 1990. Vol.2: Abstract.                               |  |
| 54 | Barber et al. "Insulin Rescues Retinal Neurons From Apoptosis by A Phosphatidylinositol 3-Kinase/Akt-Mediated Mechanism That Reduces the Activation of Caspase-3", <i>The Journal of Biological Chemistry</i> , 276(350): 32814-32821, 2001.                 |  |
| 55 | Bijur et al. "Glycogen Synthase Kinase-3 $\beta$ Facilitates Staurosporine- and Heat-Induced Apoptosis", <i>The Journal of Biological Chemistry</i> , 275(11): 7583-7590, 2000.                                                                              |  |
| 56 | Burke et al. "Potent Inhibition of Insulin Receptor Dephosphorylation by A Hexamer Peptide Containing the Phosphotyrosyl Mimetic F2Pmp", <i>Biochemical and Biophysical Research Communications</i> , 204(1): 129-134, 1994.                                 |  |
| 57 | Burke et al. "4'-O[2(2-Fluoromalonyl)]-L-Tyrosine: A Phosphotyrosyl Mimic for the Preparation of Signal Transduction Inhibitory Peptides", <i>J. Med. Chem.</i> , 39: 1021-1027, 1996.                                                                       |  |
| 58 | Burke et al. "Small Molecule Interactions With Protein-Tyrosine Phosphatase PTP1B and Their Use in Inhibitor Design", <i>Biochemistry</i> , 35: 15989-15996, 1996.                                                                                           |  |
| 59 | Chen et al. "Why Is Phosphonodifluoromethyl Phenylalanine A More Potent Inhibitory Moiety Than Phosphonomethyl Phenylalanine Towards Protein-Tyrosine                                                                                                        |  |



|    |  |                                                                                                                                                                                                                                                                                        |  |
|----|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|    |  | Phosphatase, Biochemical and Biophysical Research Communications, 216(3): 976-984, 1995.                                                                                                                                                                                               |  |
| 60 |  | Cheng et al. "'Insulin-Like' Effects of Lithium Ion on Isolated Rat Adipocytes L. Stimulation of Glycogenesis Beyond Glucose Transport", Molecular and Cellular Biochemistry, 56: 177-182, 1983.                                                                                       |  |
| 61 |  | Chu et al. "Sequential Phosphorylation by Mitogen-Activated Protein Kinase and Glycogen Synthase Kinase 3 Represses Transcriptional Activation by Heat Shock Factor-1", The Journal of Biological Chemistry, 271(48): 30847-30857, 1996.                                               |  |
| 62 |  | Cross et al. "Inhibition of Glycogen Synthase Kinase-3 by Insulin Mediated by Protein Kinase B", Nature, 378: 785-789, 1995.                                                                                                                                                           |  |
| 63 |  | Cross et al. "Selective Small-Molecule Inhibitors of Glycogen Synthase Kinase-3 Activity Protect Primary Neurons From Death", Journal of Neurochemistry, 77: 94-102, 2001.                                                                                                             |  |
| 64 |  | Crowder et al. "Glycogen Synthase Kinase-3 $\beta$ Activity Is Critical for Neuronal Death Caused by Inhibiting Phosphatidylinositol 3-Kinase or Akt But Not for Death Caused by Nerve Growth Factor Withdrawal", The Journal of the Biological Chemistry, 275(44): 34266-34271, 2000. |  |
| 65 |  | Dajani et al. "Crystal Structure of Glycogen Synthase Kinase 3 $\beta$ : Structural Basis for Phosphate-Primed Substrate Specificity and Autoinhibition", Cell, 105: 721-732, 2001.                                                                                                    |  |
| 66 |  | Devlin et al. "Textbook of Biochemistry With Clinical Correlation", Wiley-Liss, 4th Ed., XVII-XXV, 1997.                                                                                                                                                                               |  |
| 67 |  | Dugas et al. "Bioorganic Chemistry of the Amino Acids: Chemical Synthesis of Proteins", Springer Verlag, NY, P. 54-92, 1981.                                                                                                                                                           |  |
| 68 |  | Eldar-Finkelman et al. "Expression and Characterization of Glycogen Synthase Kinase-3 Mutants and Their Effect on Glycogen Synthase Activity in Intact Cells", Proc. Natl. Acad. Sci. USA, 93(19): 10228-10233, 1996.                                                                  |  |
| 69 |  | Eldar-Finkelman et al. "Phosphorylation of Insulin Receptor Substrate 1 by Glycogen Synthase Kinase 3 Impairs Insulin Action", Proc. Natl. Acad. Sci. USA, 94(18): 9660-9664, 1997.                                                                                                    |  |
| 70 |  | Eldar-Finkelman et al. "Increased Glycogen Synthase Kinase-3 Activity in Diabetes- and Obesity-Prone C57BL/6J Mice", Diabetes, 48(8): 1662-1666, 1999.                                                                                                                                 |  |
| 71 |  | Fiol et al. "Formation of Protein Kinase Recognition Sites by Covalent Modification of Substrate. Molecular Mechanism for the Synergistic Action of Casein Kinase II and Glycogen Synthase Kinase 3", J. Biol. Chem., 262(29): 14042-14048, 1987.                                      |  |
| 72 |  | Fiol et al. "Phosphoserine as A Recognition Determinant for Glycogen Synthase Kinase-3: Phosphorylation of A Synthetic Peptide Based on the G-Component of Protein Phosphatase-1", Arch. Biochem. Biophys., 267(2): 797-802, 1988.                                                     |  |
| 73 |  | Fiol et al. "A Secondary Phosphorylation of CREB341 at Ser129 Is Required for the cAMP-Mediated Control of Gene Expression. A Role for Glycogen Synthase Kinase-3 in the Control of Gene Expression", J. Biol. Chem., 269(51): 32187-32193, 1994.                                      |  |
| 74 |  | Fu et al. "Design and Synthesis of A Pyrodione-Based Phosphotyrosine Mimetic", Bioorg. Med. Chem. Lett., 8(19): 2813-2816, 1998.                                                                                                                                                       |  |
| 75 |  | Gao et al. "Inhibition of Grb2 SH2 Domain Binding by Non-Phosphate-Containing Ligands. 2,4-(2-Malonyl)Phenylalanine as A Potent Phosphotyrosyl Mimetic", J. Med. Chem., 43(5): 911-920, 2000.                                                                                          |  |
| 76 |  | Gething et al. "Cell-Surface Expression of Influenza Haemagglutinin From A Cloned DNA Copy of the RNA Gene", Nature, 293(5834): 620-625, 1981.                                                                                                                                         |  |
| 77 |  | Groves et al. "Structural Basis for Inhibition of the Protein Tyrosine Phosphatase 1B by Phosphotyrosine Peptide Mimetics", Biochemistry, 37(51): 17773-17783, 1998.                                                                                                                   |  |
| 78 |  | Hallstrom et al. "Regulation of Transcription Factor Pdr1p Function by An Hsp70 Protein in Saccharomyces Cerevisiae", Mol. Cell Biol., 18(3): 1147-1155, 1998.                                                                                                                         |  |
| 79 |  | Hanger et al. "Glycogen Synthase Kinase-3 Induces Alzheimers Disease-Like Phosphorylation of Tau: Generation of Paired Helical Filament Epitopes and Neuronal Localisation of the Kinase", Neuroscience Letters, 147: 58-62, 1992.                                                     |  |
| 80 |  | Hawiger "Cellular Import of Functional Peptides to Block Intracellular Signaling", Curr. Opin. Immunol., 9(2): 189-194, 1997.                                                                                                                                                          |  |
| 81 |  | He et al. "Glycogen Synthase Kinase-3 and Dorsoventral Patterning in Xenopus Embryos", Nature, 374(6523): 617-622, 1995.                                                                                                                                                               |  |
| 82 |  | Higashimoto et al. "Human P53 Is Phosphorylated on Serines 6 and 9 in Response to DNA Damage-Inducing Agents", J. Biol. Chem., 275(30): 23199-23203, 2000.                                                                                                                             |  |
| 83 |  | Klein et al. "A Molecular Mechanism for the Effect of Lithium on Development",                                                                                                                                                                                                         |  |



|     |  |                                                                                                                                                                                                                                                |  |
|-----|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|     |  | Proc. Natl. Acad. Sci. USA, 93: 8455-8459, 1996.                                                                                                                                                                                               |  |
| 84  |  | Kole et al. "Protein-Tyrosine Phosphatase Inhibition by A Peptide Containing the Phosphotyrosyl Mimetic, L-O-Malonyltyrosine", Biochem. Biophys. Res. Commun., 209(3): 817-822, 1995.                                                          |  |
| 85  |  | Kole et al. "Specific Inhibition of Insulin Receptor Dephosphorylation by A Synthetic Dodecapeptide Containing Sulfotyrosyl Residues as Phosphotyrosyl Mimetic", Indian. J. Biochem. Biophys., 34(1-2): 50-55, 1997.                           |  |
| 86  |  | Latimer et al. "Stimulation of MAP Kinase by V-Raf Transformation of Fibroblasts Fails to Induce Hyperphosphorylation of Transfected Tau", FEBS Lett., 365: 42-46, 1995.                                                                       |  |
| 87  |  | Lucas et al. "Decreased Nuclear Beta-Catenin, Tahyperphosphorylation and Neurodegeneration in GSK-3Beta Conditional Transgenic Mice", EMBO J., 20:27-39, 2001.                                                                                 |  |
| 88  |  | Lovestone et al. "Alzheimer's Disease-Like Phosphorylation of the Microtubule-Associated Protein Tau by Glycogen Synthase Kinase-3 in Transfected Mammalian Cells", Current Biology, 4: 1077-1086, 1995.                                       |  |
| 89  |  | Mandelkow et al. "Tau as A Marker for Alzheimer's Disease", Trends Biochem. Sci., 18(12): 480-483, 1983.                                                                                                                                       |  |
| 90  |  | Mandelkow et al. "Glycogen Synthase Kinase-3 and the Alzheimer-Like State of Microtubule-Associated Protein Tau", FEBS Letters, 314: 315-321, 1992.                                                                                            |  |
| 91  |  | Manji et al. "Lithium at 50: Have the Neuroprotective Effects of This Unique Cation Been Overlooked?", Biol. Psychiatry, 46(7): 929-940, 1999.                                                                                                 |  |
| 92  |  | McKinsey et al. "Phosphorylation of the PEST Domain of IkappaBbeta Regulates the Function of NF-KappaB/IkappaBbeta Complexes", J. Biol. Chem., 272(36): 22377-22380, 1997.                                                                     |  |
| 93  |  | Merrifield et al. "Solid Phase Peptide Synthesis. I. The Synthesis of A Tetrapeptide", J. Am. Chem. Soc., 85: 2149-2154, 1963.                                                                                                                 |  |
| 94  |  | Mikol et al. "The Crystal Structures of the SH2 Domain of P56lck Complexed With Two Phosphonopeptides Suggest A Gated Peptide Binding Site", J. Mol. Biol., 246(2): 344-355, 1995.                                                             |  |
| 95  |  | Morrison et al. "Organic Chemistry", Allyn and Bacon, 5th Ed., V-XXIV, 1987.                                                                                                                                                                   |  |
| 96  |  | Mulot et al. "PHF-Tau From Alzheimer's Brain Comprises Four Species on SDS-PAGE Which Can Be Mimicked by In Vitro Phosphorylation of Human Brain Tau by Glycogen Synthase Kinase-3 Beta", FEBS Lett., 349(3): 359-364, 1994.                   |  |
| 97  |  | Mulot et al. "Phosphorylation of Tau by Glycogen Synthase Kinase-3 Beta In Vitro Produces Species With Similar Electrophoretic and Immunogenic Properties to PHF-Tau From Alzheimer's Disease Brain", Biochem. Soc. Trans., 23(1): 45S, 1995.  |  |
| 98  |  | Myers et al. "IRS-1 Activates Phosphatidylinositol 3'-Kinase by Associating With SRC Homology 2 Domains of P85D", Proc. Natl. Acad. Sci. USA, 89(21): 10350-10354, 1992.                                                                       |  |
| 99  |  | Nicolaou et al. "Design and Synthesis of A Peptidomimetic employing $\beta$ -D-Glucose for Scaffolding", Peptides, ESCOM, 1990.                                                                                                                |  |
| 100 |  | Nikoulina et al. "Regulation of Glycogen Synthase Activity in Cultured Skeletal Muscle Cells From Subjects With Type II Diabetes: Role of Chronic Hyperinsulinemia and Hyperglycemia", Diabetes, 46(6): 1017-1024, 1997.                       |  |
| 101 |  | Nikoulina et al. "Potential Role of Glycogen Synthase Kinase-3 in Skeletal Muscle Insulin Resistance of Type 2 Diabetes", Diabetes, 49(2): 263-271, 2000.                                                                                      |  |
| 102 |  | Nonaka et al. "Chronic Lithium Treatment Robustly Protects Neurons in the Central Nervous System Against Excitotoxicity by Inhibiting N-Methyl-D-Aspartate Receptor-Mediated Calcium Influx", Proc. Natl. Acad. Sci. USA, 95: 2642-2647, 1998. |  |

|           |  |            |  |
|-----------|--|------------|--|
| Signature |  | Considered |  |
|-----------|--|------------|--|

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup>. Applicant's unique citation designation number (optional). <sup>2</sup>. Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. this collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

**SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*